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Methods: 24 clinicians, ("non-expert MD", n = 16; "non-expert non-MD"; n = 4; and oral "expert", n = 4), from six major transplant centers scored high-quality intraoral photographs of 12 patients. The same photographs were evaluated 1 week later by the same evaluators. An intra-class correlation coefficient (ICC) was used to calculate intra-rater reliability and inter-rater agreement was analyzed using a weighted κ statistic: $0 \leq \kappa \leq 0.20$ = poor, $0.21 \leq \kappa \leq 0.40$ = fair, $0.41 \leq \kappa \leq 0.60$ = moderate, $0.61 \leq \kappa \leq 0.80$ = good, $0.81 \leq \kappa \leq 1.00$ = very good. Data on participant experiences and demographics were also collected.

Results: Mean inter-rater reliability for each element was poor to moderate (range 0.15 – 0.46). Overall mean kappa scores were highest for ULCERS (0.46), followed by ERYTHEMA (0.23) and lowest for LICHENOID (0.15) and MUCOCELES (0.14). Kappa scores were higher in "expert" compared with "non-expert MD" and "non-expert non-MD" in ULCERS and ERYTHEMA (e.g. 0.85, 0.44, 0.33 for ULCERS, respectively), but similar in LICHENOID and MUCOCELES. Overall intra-rater reliability in all groups was very good (≥0.90) and highest for ULCERS (0.97, 0.85, 0.94). While 75% of "experts" were *comfortable* with their abilities to score the cases, approximately 50% of "non-experts" were *uncomfortable*. The majority felt that their evaluations were *accurate*, however 84% agreed that *formal training is required*.

Conclusions: Inter-rater variability of the oral cGVHD instrument is unacceptable for the purposes of clinical trials. Greater concordance among "experts", high intra-rater reliability, and participant feedback suggests that formal training may significantly decrease variability. Parallel investigations must be completed using the other organ specific instruments prior to any revision and widespread prospective utilization of these tools as research endpoints.

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INTERACTIONS BETWEEN DC AND T-CELLS INITIATE COUNTER-REGULATORY IMMUNE ACTIVITIES THAT LIMITS AMPLIFICATION OF ALLO-IMMUNE RESPONSES AND GvHD

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Acute graft-versus-host disease (GvHD) remains a major complication following allogenic hematopoietic stem cell transplant (HSCT). Our reports and several publications have suggested a potential beneficial effect of donor DC during HSCT. Using allogeneic MHC-mismatched HSCT mice model, we previously demonstrated that recipients transplanted with FACS-purified CD11b$^-$ DC with HSC and T-cells had increased GvL and limited GvHD. In the current study, we found that transplantation of T-cells from IFN-γ *knock-out* mice resulted in severe GvHD and higher levels of Th17 cells compared with recipients of T-cells from wide-type (WT) mice, suggesting that donor T-cell synthesis of IFN-γ induced by donor DC is necessary to augment expansion of allo-reactive T-cells that mediate GvL while subsequently limiting generalized activation of donor T-cells that lead to off-target effects and GvHD. In order to further clarify the mechanisms involved in the action of donor DC on the limitation of GvHD, we detected the level of the IFN-γ-inducible indoleamine-2,3-dioxygenase(IDO) protein, which has been reported to exert inhibitory effects on T cells activity, on donor DCs and its potential roles in regulating donor T cell allo-immune activity. We set up an *in vitro* co-culture system including purified CD11b$^-$ DC from WT or IDO *knock-out* mice and CFSE-labeled syngeneic T cells in the presence of allogeneic antigen. T-cells co-cultured with CD11b$^-$ DC had higher proliferation rates compared with T-cells cultured with allo-antigen in the absence of DCs. Furthermore, CD8 T-cells proliferated earlier and more than CD4 T-cells in response to alloantigen in the presence of CD11b$^-$ DC, suggesting CD8 T-cells be mainly responsible for the observed GvL activity in murine model systems. IDO expression on WT CD11b$^-$ DC was increased in 3–7 day cultures containing syngeneic T cells and allo-antigen but not on DC cultured with allo-antigen alone. Thus, IFN-γ-induced IDO expression on CD11b$^-$ donor DCs might be a critical downstream event that inhibits continued T-cell activation by initiating counter-regulatory immune activities that limit allo-immune responses. Interestingly, T cells co-cultured with CD11b$^+$ DC from IDO *knock-out* donors had higher proliferation rate than T cells co-cultured with CD11b$^-$ DC on day-7. Further studies using IDO *knock-out* mice as DC donors in our C57BL/6→B10.BR transplant model are essential to understand the role of IDO expression of DC in allogeneic HSCT.

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INHIBITION OF GSK3 AND mTOR ENHANCES THE STEMNESS OF ACTIVATED CD8$^+$ T CELLS

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Memory T cells have the ability to vigorously proliferate and to generate differentiated effector cells upon reencounter of the cognate antigen, while self-renewing. This stemness property of memory T cells has been explored for adoptive T cell immunotherapy. On the other hand, it may be particularly difficult to treat memory T cell-mediated inflammatory disorders, such as graft-versus-host disease (GVHD) among others, unless long-lived memory T cells are effectively targeted. However, the molecular mechanisms that regulate the stemness of memory T cells remain unknown. Using mouse GVHD models, we have previously identified a population of alloreactive postmitotic CD44^{lo}CD62L^{hi}CD8$^+$ memory T cells (T_{PM}) that induce GVHD. These T_{PM} cells are able to generate all subsets of effector and memory T cells and have greater ability than both effector memory T cells (T_{EM}) and central memory T cells (T_{CM}) to proliferate, while self-renewing. These data suggest that T_{PM} cells contain higher frequency of T memory stem cells than other memory T cell subsets. In the present study, we found that these T_{PM} cells were initially generated during host antigen-priming of donor T cells and persisted throughout the disease course. Gene microarray analysis revealed that T_{PM} cells represented the earliest antigen-experienced CD8$^+$ T cells to become effector and memory T cells, whereas T_{EM} cells were terminally differentiated cells. As comparison, T_{CM} cells were the intermediates between T_{PM} cells and T_{EM} cells. Interestingly, during differentiation of T_{PM} cells to T_{EM} cells, Wnt-signaling activity was dramatically decreased, whereas mTOR activity was augmented. A similar molecular profiling of alloreactive T cells was also found in activated TCR-transgenic CD8$^+$ T cells specific to LCMV gp33 peptide. Inhibition of either GSK3 or mTOR during antigenic-priming of CD8$^+$ T cells significantly enhanced the generation of memory T cells specific to gp33 peptide. Thus, both GSK3- and mTOR-mediated signals play important roles in regulating the stemness of activated CD8$^+$ T cells. These findings have significant implications in the development of new methods to treat ongoing GVHD and to augment adoptive T cell cancer therapy.

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OPTIMIZATION OF ALEMTUZUMAB DOSE FOR GRAFT-VERSUS-HOST DISEASE PROPHYLAXIS FOR REDUCED INTENSITY TRANSPLANTATION FROM UNRELATED DONORS FOR PATIENTS WITH HEMATOLOGIC MALIGNANCIES

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It has been shown that a high dose of alemtuzumab (100mg) in combination with cyclosporine (CsA) significantly reduces the risk of acute and chronic GVHD, however a high risk of relapse compromises the transplant outcomes. We hypothesized that a lower dose of alemtuzumab for GVHD prophylaxis may help in achieving a balance between prevention of severe GVHD while preserving a Graft-versus-leukemia (GVL) effect. We studied the use of a lower dose of alemtuzumab with CsA as GVHD prophylaxis in 36 patients undergoing reduced intensity conditioning (RIC) using matched unrelated donors. The study includes two sequential cohorts treated at Princess Margaret Hospital between September 2004 and July 2007: cohort 1 (n = 17) received 60 mg of IV alemtuzumab (10mg, 20mg and 30 mg on days –8, −7 and –6); cohort 2 (n = 19) received 30 mg